Systemic delivery of factor IX messenger RNA for protein replacement therapy.

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Public Summary:
Hemophilia B is a bleeding disorder caused by a lack of coagulation factor IX (FIX) in the plasma and affects around 1 in 30,000 males. Patients with dysfunctional FIX protein are unable to form normal clots and are susceptible to life-threatening bleeds. They also suffer from recurrent bleeding into joints that leads to significant pain, deformities and loss of mobility. Current treatment (based on FIX protein infusion) is transient and plagued by increased risk for blood-borne infections (HCV, HIV etc.), high costs, and limited availability. Currently Hemophilia B patients are treated prophylactically or after a bleed with intravenous dosing of plasma-derived or recombinant hFIX protein. While these products are 90% effective in stopping hemorrhages, they have a short half-life and must be given 2-3 times/week to prevent hemorrhages and arthropathies. This means that patients require indwelling venous ports and are at risk for developing infection, sepsis and thrombosis. The treatment is also prohibitively expensive, especially in developing countries. This has fueled a search for alternatives such as gene and cell therapy. Use of viral vectors for gene therapy has been shown to be effective but it is plagued with safety concerns and problems immunogenicity. Being the natural site of FIX synthesis, the liver is envisaged to promote immune-tolerance and provide easy access to circulation. Liver transplantation is thus a successful, long-term therapeutic option but is limited by availability of donor livers and long-term immunosuppression. This makes iPSC-based cell therapy an attractive prospect. However, cell therapy with iPSCs is challenging and despite much progress, we are farther out from clinical use. Another therapeutic approach is developing better gene therapy based approaches that can mitigate the risks of viral vectors. Safe and efficient delivery of messenger RNAs for protein replacement therapies offers great promise but remains challenging. Despite the advantages over DNA and viral vectors, RNA-based therapeutics have been plagued by problems of poor translatability, stability and adverse immune reactions. Efficient in vivo delivery has also been challenging since currently available lipid nanoparticles (LNPs) can induce liver damage and elicit a strong immune response. In our 2017 study, we demonstrated the successful use of LUNARTM - a safe, reproducible and effective LNP mRNA delivery platform that can be used to treat diseases requiring protein replacement. Delivery of hFIX mRNA encapsulated in our LNPs resulted in a rapid pulse of FIX protein (within 4-6 hrs) that remained therapeutically effective for 4-6 days and performed comparably to the rhFIX protein (current standard of care). Extensive cytokine and liver enzyme profiling showed that repeated administration of the mRNA-LUNARTM complex does not cause any adverse innate or adaptive immune responses in immune-competent, hemophilic mice. These results suggest that delivery of long mRNAs is a viable therapeutic alternative for many clotting disorders and for other hepatic diseases where recombinant proteins may be unaffordable or unsuitable. Also, its versatility and broad applicability from a therapeutic standpoint make it an attractive avenue to pursue.

Scientific Abstract:
Safe and efficient delivery of messenger RNAs for protein replacement therapies offers great promise but remains challenging. In this report, we demonstrate systemic, in vivo, nonviral mRNA delivery through lipid nanoparticles (LNPs) to treat a Factor IX (FIX)-deficient mouse model of hemophilia B. Delivery of human FIX (hFIX) mRNA encapsulated in our LUNAR LNPs results in a rapid pulse of FIX protein (within 4-6 h) that remains stable for up to 4-6 d and is therapeutically effective, like the recombinant human factor IX protein (rhFIX) that is the current standard of care. Extensive cytokine and liver enzyme profiling showed that repeated administration of the mRNA-LUNAR complex does not cause any adverse innate or adaptive immune responses in immune-competent, hemophilic mice. The levels of hFIX protein that were produced also remained consistent during repeated administrations. These results suggest that delivery of long mRNAs is a viable therapeutic alternative for many clotting disorders and for other hepatic diseases where recombinant proteins may be unaffordable or unsuitable.